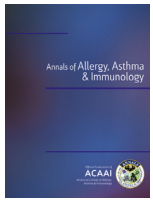
Ann Allergy Asthma Immunol xxx (2013) 1–4

Contents lists available at ScienceDirect



Perspective

Aspirin allergy in patients with myocardial infarction: the allergist's role

Kathryn L. McMullan, MD

Division of Clinical Immunology and Allergy, Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi

ARTICLE INFO

Article history:
Received for publication August 10, 2013.
Received in revised form November 5, 2013.
Accepted for publication November 24, 2013.

Introduction

Drug hypersensitivity can preclude patients from receiving the drug of choice to treat a specific illness. In some cases, such as penicillin allergy in a pregnant woman with syphilis,[1] the drug is clearly indicated, and allergists may be called on to induce temporary drug tolerance (desensitize). In other cases, the medication benefit is not as clear, and allergists must weigh desensitization (DS) risks against the risks and benefits of alternative medications. For aspirin (ASA) hypersensitivity, a significant amount of literature has been published addressing scenarios in which patients with aspirin-exacerbated respiratory disease (AERD) are desensitized to ASA, but little has been published to address the issue of ASA hypersensitivity in patients with other types of ASA hypersensitivity and myocardial infarction (MI). Of the protocols for these patients that have been published, none have been prospectively randomized, validated, or clearly documented to alter the immune system, making the diagnosis and treatment pathway unclear at times. ASA is clearly of benefit in patients with ST-segment elevation MI (STEMI) or non-STEMI.[2] In patients who tolerate ASA, ASA therapy is expected; other antiplatelet agents are additions, not substitutions.[3] In the era of dual antiplatelet therapy, allergists can offer cardiology colleagues a valuable service if called on to evaluate patients reporting ASA hypersensitivity.

ASA Hypersensitivity Epidemiology and Categories

The prevalence of patients with MI reporting ASA hypersensitivity is not clearly defined. A recent study has reported 1.5% of the cardiac population giving a history of ASA adverse events, with only 21% of these patients having a history compatible with ASA hypersensitivity.[4] Another study has noted 2.6% of patients admitted for cardiac catheterization with ASA hypersensitivity.[5] This percentage of the cardiac population is manageable for allergists desiring to incorporate ASA evaluations, graded challenges, and DSs into their consultative service repertoire if not already provided.

Aspirin hypersensitivity can generally be grouped into 4 categories: (1) rhinitis and asthma induced by nonsteroidal anti-inflammatory drugs (NSAIDs), (2) chronic urticaria or angioedema induced by NSAIDs, (3) urticaria or angioedema induced by multiple NSAIDs, and (4) single NSAID-induced reactions[6] Type 1 generally refers to AERD. Patients are sensitive to all NSAIDs, and it is mediated by the cyclooxygenase (COX)-1 mechanism. Other categories typically displaying cross-reactivity to COX-1–inhibiting NSAIDS include types 2 and 3.[7] Type 4 is thought to be possibly mediated by IgE. Some patients have a mixed presentation and do not fit neatly into a specific category.[6,8] Many patients who cannot take COX-1 inhibitors can take COX-2 inhibitors, but these are not a substitute for ASA in patients who have had MI.

Graded Challenge vs DS

The difference between a diagnostic, multistep graded challenge and DS can be a bit hazy, particularly when it comes to ASA. In general, graded challenges are meant to diagnose or rule out drug allergy, whereas DS is undertaken to alter the immune system and render effector cells less reactive by administering increasing doses of the medication.[1,9] Tolerance is temporary but should last as long as there is continued administration of the drug.[9] DSs for patients with AERD are somewhat different and combine the principles of a graded challenge and DS: a critical portion of the DS procedure is the demonstration of a mild respiratory reaction, thus proving the hypersensitivity and placing the patient in a refractory state so that DS can be completed.[9] For patients with type 2 to 4 ASA hypersensitivity, whether DS should elicit hypersensitivity symptoms is not clear.[9] For other medication classes, such as antibiotics, DS is possible to complete without any manifestations of hypersensitivity.[1,9] According to the 2010 drug allergy practice parameters, it is thought that graded drug challenges of more than 4 or 5 steps may induce drug tolerance (desensitize)[9]; thus, there is a gray area determining crossover from a graded challenge to DS. It would seem reasonable that this gray area could be avoided by designing diagnostic graded challenges with no more than 3 steps and DSs with at least 6 steps, although this approach could be debated. These controversies do not apply to patients with AERD.

Reprints: Kathryn L. McMullan, MD, 2500 North State Street, Jackson, MS 39216; E-mail: klmcmullan@umc.edu.

Disclosures: Author has nothing to disclose.

http://dx.doi.org/10.1016/j.anai.2013.11.020

Table 1
Outpatient multiday protocol[a] for patients with asthma-exacerbated respiratory disease[10]

Step	Day	Time (h)	Dose (mg)	Cumulative dose (mg)
1	1	0	20.25[b]	20.25
2	1	3	60.75	81
3	1	6	81	162
4	2	0	101.25	263.25
5	2	3	162.5	425.75
6	2	6	325	750.75

[a]Vital signs and forced expiratory volume in 1 second are measured each hour. Reactions typically occur with doses of 20 to 101 mg. After stabilization, the dose should be repeated and the patient monitored for 3 additional hours. This may occur on day 1 or 2. If, on day 1, nasal, gastrointestinal, or cutaneous reactions occur, the patient should be pretreated with H_1 and H_2 receptor blockers for the remainder of the procedure. See text for further details.
[b]Alternatively, the initial dose may be 40.25 mg. The cumulative dose would be 770.75 mg if the procedure began at this point.

Table 2
Rapid outpatient protocol[a,15]

Step	Dose (mg)	Volume (mL)[b]	Cumulative dose (mg)
1	1	0.1	1
2	10	1	11
3	20	2	31
4	40	4	71
5	80	8	151
6	160	16	311
7	325	entire tablet	636

[a]Doses are administered 15 minutes apart. The protocol can be performed in inpatients and outpatients.
[b]Volume was obtained by dissolving 1 Alka-Seltzer tablet (contains 325 mg of aspirin; Bayer Healthcare, Bayer Consumer Care, Morristown, New Jersey) in 32.5 mL of water for a 10-mg/mL solution. See text for further details.

The combination of a diagnostic graded challenge and DS has been well established, and specific protocols have been well studied.[9,10]

In patients with MI and good histories for true ASA hypersensitivity, the rationale behind going straight to DS is the concern that positive graded challenges might exacerbate the underlying coronary artery disease.[1,5,7] This approach is controversial. Some cite ASA as a cause of anaphylaxis,[11,12] whereas others maintain that anaphylaxis to ASA does not exist in patients without AERD.[13] Perhaps in a patient without AERD, the greatest risk of a positive reaction would be that of cutaneous symptoms, but some allergists may desire to take a more cautious approach and proceed with DS instead of a graded challenge. Time and resources are spent on this approach, and then the patient is required to take daily ASA, undergoing repeat DS if a break in ASA therapy occurs. Fortunately, this is a patient population in which daily ASA is desirable.

If the evaluating allergist judges a diagnostic graded challenge to be safe in a particular patient and the potential for histamine-mediated exacerbation of the underlying cardiac disease to be low, then this would be the preferred procedure. However, if a more cautious approach of going straight to DS seems warranted, rapid DS protocols provide options to get ASA on board quickly and safely in patients without AERD. The problem with rapid protocols is that they are not validated, and their immunomodulating potential has not been appropriately documented. Conversely, their lengths preclude them from clearly being negative diagnostic graded challenges if completed without reaction. Despite these issues, they have been reported to be safe and successful in patients with good histories for ASA allergy and cardiac disease; patients continue to do well on ASA after these procedures. Patients with MI and type 2 to 4 ASA hypersensitivity provide a unique challenge; until such time as these issues are better elucidated, practicing allergists should be aware of the options that exist, although imperfect.

Should the allergist decide to proceed with DS, there are several protocols to choose from. Patients with histories indicative of AERD should be desensitized using a slow, multiday protocol. A small series of patients with AERD and coronary disease has been reported to be safely desensitized.[7] The Scripps Clinic protocol may be used in inpatients or outpatients with AERD; it takes 2 to 4 days to complete[10] (Table 1). Patients with MI reporting other types of ASA hypersensitivity may undergo rapid oral DS procedures, completing them in the course of a few hours.[5,7,14–16] Only 1 of these rapid protocols has been used in the outpatient setting[15] (Table 2). Table 3 presents an example of a rapid protocol used in the inpatient setting. Randomized trials have not been performed on rapid protocols. Rapid protocols begin with small doses of ASA, such as 0.1 or 1 mg. Although not common, objective hypersensitivity symptoms have been documented to small doses of ASA.[14,15,17] Typically, however, patients do well during rapid procedures. Success rates for DS on the first attempt are high: 88.5%,[5] 87.5%,[16] 81.8%,[14] and 91.3%,[15] although not all in the last group had MI. Not only were the initial success rates good, patients continued to tolerate ASA in these series. In the first 3 series, follow-up ranged from 1 to 24 months, with only 2 patients discontinuing ASA owing to mild symptoms. In the last series, follow-up was not completed for all patients, but only 2 patients were noted to discontinue ASA owing to hypersensitivity symptoms, also mild. Other reasons patients discontinued ASA included peptic ulcer[5] and noncardiac surgery.[16] Hypersensitivity symptoms necessitating discontinuation of DS were usually mild. Because the immunomodulating potential of these protocols is unknown, these patients may not have been hypersensitive to ASA. McMullan and Wedner[15] reported patients who safely completed a rapid protocol despite hypersensitivity symptoms during DS.

ASA Benefit in Patients with MI

Because allergists may be asked to assist in the evaluation and possible DS of patients with MI reporting ASA hypersensitivity, awareness of current cardiology recommendations is beneficial. Table 4 lists recommendations for ASA therapy in patients with unstable angina or non-STEMI.[3] Attempting DS in ASA-hypersensitive patients treated medically without stenting is briefly mentioned, but no further recommendations on this point are given. Dosing tables indicate that all patients are to receive ASA; other medications are considered additional.[3]

Table 4 also lists current recommendations for ASA therapy in patients with STEMI. Neither ASA hypersensitivity nor alternative therapy is mentioned.[18] In the most current percutaneous coronary intervention (PCI) guidelines, ASA DS is no longer mentioned. In 2005 it was mentioned that ASA DS could be performed in select patients, but no other information was given.[19,20] The STEMI guidelines and guidelines for those undergoing PCI give a class III

Table 3
Rapid inpatient protocol[a,14]

Step	Dose (mg)	Cumulative dose (mg)
1	0.1	0.1
2	0.3	0.4
3	1	1.4
4	3	4.4
5	10	14.4
6	20	34.4
7	40	74.4
8	81	155.4
9	162[b]	317.4
10	325[b]	642.4

[a]Doses are administered at 10- to 20-minute intervals.
[b]Doses noted to be optional depending on the desired final dose of aspirin. See text for further details.

Table 4
Indications for ASA in patient with UA, NSTEMI, and STEMI[3,14]

Recommendation	Patient population	Class[a]	Level of evidence[b]
Start ASA in patients who tolerate it as soon as possible after hospital presentation and continue indefinitely	UA/NSTEMI	I	A
Start ASA on presentation in medium- to high-risk patients if no hypersensitivity and invasive strategy is planned in conjunction with a second antiplatelet agent	UA/NSTEMI	I	A[c]
In patients with ASA hypersensitivity, initiate an alternative antiplatelet such as	UA/NSTEMI	I	
Clopidogrel			B
Prasugrel			C
Ticagrelor			C
Continue ASA indefinitely in patients with UA/NSTEMI after stress testing, considered low risk, in whom no invasive strategy is planned	UA/NSTEMI	I	A
If CABG is planned, ASA should be continued	UA/NSTEMI	I	A
If medical management planned and	UA/NSTEMI	I	
If here is no significant CAD found at angiography, continue ASA at clinician's discretion			C
If there is evidence of atherosclerosis but no flow-limiting lesions, continue ASA			C
If CAD is found, continue ASA			A
If no angiography or stress testing performed, continue ASA			A
Long-term ASA therapy should be given to patients without hypersensitivity indefinitely with or without a stent	UA/NSTEMI	I	A
Long-term antiplatelet therapy in patients with ASA hypersensitivity should be given with	UA/NSTEMI	I	
Clopidogrel			B
Prasugrel			C
Ticagrelor			C
Long-term ASA therapy may be given at the dose of 81 mg/d after PCI	UA/NSTEMI	IIa	B
Load with 162–325 mg of ASA in patients who receive fibrinolysis	STEMI	I	A
Continue ASA at 81–325 mg/d indefinitely after fibrinolysis	STEMI	I	A
ASA 81 mg/d as preferred maintenance dose after fibrinolysis	STEMI	IIa	B
ASA 81–325 mg/d after PCI indefinitely	STEMI	I	A
ASA 162- to 325-mg load before primary PCI	STEMI	I	B
ASA 162- to 325-mg load given with fibrinolysis before PCI	STEMI	I	A
ASA 81- to 325-mg/d maintenance after PCI	STEMI	I	A
ASA 81 mg/d as preferred maintenance dose	STEMI	IIa	B
If urgent CABG required, do not withhold ASA	STEMI	I	C
For pericarditis after STEMI, ASA is recommended	STEMI	I	B
If patient cannot tolerate dual antiplatelet therapy for 1 y, drug-eluting stent should not be used	STEMI, patients undergoing PCI[15]	III, harm	B

Abbreviations: ASA, aspirin; CABG, coronary artery bypass grafting; CAD, coronary artery disease; NSTEMI, non–ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

[a]Class I, benefit >>> risk, procedure/treatment should be performed/administered; class IIa, benefit >> risk, it is reasonable to perform procedure/administer treatment; class IIb, benefit ≥ risk, procedure/treatment may be considered; class III, no benefit, procedure/test is not helpful, treatment has no proved benefit; class III, harm, procedure/test causes excess cost without benefit or procedure/test is harmful, treatment is harmful.

[b]A, multiple populations evaluated, multiple randomized controlled trials or meta-analyses; B, limited populations evaluated, single randomized trial or nonrandomized studies; C, very limited populations evaluated, consensus opinion of experts, case studies, or standard of care. For each level of evidence in conjunction with class I, usefulness/effectiveness established; in conjunction with class II, (a) some conflicting evidence exists and usefulness/effectiveness is favored (b) greater conflicting evidence exists and usefulness/efficacy less well established; in conjunction with class III, no usefulness/effectiveness with possible harm.

[c]For ASA in all cases, the recommendation for each antiplatelet choice differs based on which antiplatelet is chosen.

harm recommendation for placing drug-eluting stents in patients who cannot tolerate dual antiplatelet therapy for 1 year.[18,19] DSs, although often well tolerated, are not guaranteed to be successful. Communication of such to the cardiologist might affect the intervention choice should the consultation occur before the catheterization.

Allergists also should be aware of timeline recommendations for coronary intervention in patients with STEMI. In these patients, it would not be prudent to attempt DS before catheterization. Depending on the location of the patient, PCI is recommended within 90 to 120 minutes of patient presentation (class IB), and fibrinolysis is recommended within 30 minutes.[18]

Allergists should discuss with the cardiologist whether 325 or 81 mg is the preferred daily dose for the patient before initiating DS; 81 mg/d is allowed (class IIaB).[3,18] If the patient also will be on ticagrelor, a black box warning indicates that ASA doses higher than 100 mg/d should not be used. It is thought that 81 mg/d is enough to maintain a DS.[10]

Other DS Considerations

Other factors allergists must consider when planning DS include β-blocker use and uncontrolled cardiac disease. In general, these would be contraindications to DS[1]; however, the benefits patients with MI receive from ASA outweigh these risks, and their cardiac outcome will likely be improved on ASA. It would be prudent to perform DS after these patients have achieved some level of stability to their cardiac disease, such as after a stenting procedure or initiation of medical management if no intervention is planned. Most published rapid protocols do not indicate that β-blockers were routinely withheld,[5,14,15] thus assuming that with appropriate discussion of risks and benefits before the procedure, DS can be performed despite β-blocker therapy. In certain patients, a temporary discontinuation may be possible; Silberman et al[16] did withhold β-blockers 24 hours before a procedure.

Written, informed consent should be obtained before beginning DS. In all cases, DS should be undertaken by physicians and nurses who have been trained to recognize signs of hypersensitivity.[8] If hypersensitivity symptoms occur, the reaction should be treated immediately. Depending on the severity, allergists may choose to treat through the reaction.[1] It is not recommended that premedication with systemic steroids or antihistamines be given in most cases, because early signs of hypersensitivity could be masked.[8]

Communication with the cardiologist will help establish the location of the procedure. The cardiologist likely will desire the initiation of ASA therapy while the patient is still hospitalized after PCI. In other cases, such as medical management or before elective PCI, it may be possible to arrange an outpatient evaluation with potential DS. Despite the clear benefit of ASA in patients with MI, allergists often are not consulted to evaluate and possibly

desensitize those with histories of ASA hypersensitivity.[4] This is unfortunate, because DS tends to be well tolerated, as discussed earlier. The exception tends to be patients with chronic urticaria and angioedema (type 2); they often continue to have flares of urticaria and angioedema despite DS.[5,7,14] Based on the current literature, the benefits of DS in ASA-hypersensitive patients with MI outweigh the risks. Thus, allergists can offer a valuable service to these patients and their cardiology colleagues.

Conclusion

Aspirin clearly benefits patients with MI. If the evaluating allergist deems DS necessary, case series indicate that DS can be completed rapidly, safely, and successfully in this population of patients giving reaction histories consistent with types 3 and 4 and possibly blended reactions. It stands to reason that DS can be completed safely and successfully in this population if they have AERD, although with a slower protocol. Different protocols have been published for the allergist to choose from. Further research is warranted into diagnostic techniques allowing allergists to more easily identify true ASA hypersensitivity, further elucidating the safety of a diagnostic graded challenge in this population, and to determine whether patients who complete rapid protocols are truly desensitized vs merely having passed a multistep graded challenge. Other issues that would benefit from further clarification in prospective trials include the ideal DS protocol length and safety of concomitant β-blocker treatment. In the meantime, allergists and cardiologists should work together to increase the number of patients with ASA hypersensitivity and MI who can safely take this medication.

References

[1] Cernadas JR, Brockow K, Romano A, et al. General considerations on rapid desensitization for drug hypersensitivity—a consensus statement. *Allergy*. 2010;65:1357–1366.

[2] Baigent C, Collins R, Appleby P, Parish S, Sleight P, Peto R. ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. The ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *BMJ*. 1998;316:1337–1343.

[3] Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non–ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2012;60:645–681.

[4] Feng CH, White AA, Stevenson DD. Characterization of aspirin allergies in patients with coronary artery disease. *Ann Allergy Asthma Immunol*. 2013;110:92–95.

[5] Rossini R, Angiolillo DJ, Musumeci G, et al. Aspirin desensitization in patients undergoing percutaneous coronary interventions with stent implantation. *Am J Cardiol*. 2008;101:786–789.

[6] Kowalski ML, Stevenson DD. Classification of reactions to nonsteroidal anti-inflammatory drugs. *Immunol Allergy Clin North Am*. 2013;33:135–145.

[7] Gollapudi RR, Teirstein PS, Stevenson DD, Simon RA. Aspirin sensitivity: implications for patients with coronary artery disease. *JAMA*. 2004;292:3017–3023.

[8] Khan DA, Soensky R. Drug allergy. *J Allergy Clin Immunol*. 2010;125(suppl 2):S126–S137.

[9] Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2010;105:259–273.

[10] Stevenson DD, Simon RA. Selection of patients for aspirin desensitization treatment. *J Allergy Clin Immunol*. 2006;118:801–804.

[11] Simons FE. Anaphylaxis. *J Allergy Clin Immunol* 2010;125(suppl 2):S161–S181.

[12] Kemp SF, Lockey RF, Wolf BL, Lieberman P. Anaphylaxis. A review of 266 cases. *Arch Intern Med*. 1995;155:1749–1754.

[13] Woessner KM, Simon RA. Cardiovascular prophylaxis and aspirin "allergy." *Immunol Allergy Clin North Am*. 2013;33:263–274.

[14] Wong JT, Nagy CS, Krinzman SJ, Maclean JA, Bloch KJ. Rapid oral challenge-desensitization for patients with aspirin-related urticaria–angioedema. *J Allergy Clin Immunol*. 2000;105:997–1001.

[15] McMullan KL, Wedner HJ. Safety of aspirin desensitization in patients with reported aspirin allergy and cardiovascular disease. *Clin Cardiol*. 2013;36:25–30.

[16] Silberman S, Neukirch-Stoop C, Steg PG. Rapid desensitization procedure for patients with aspirin hypersensitivity undergoing coronary stenting. *Am J Cardiol*. 2005;95:509–510.

[17] Fajt ML, Petrov AA. Outpatient aspirin desensitization for patients with aspirin hypersensitivity and cardiac disease. *Crit Pathw Cardiol*. 2011;10:17–21.

[18] O'Gara PT, Kushner FG, Ascheim DD, et al. American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61:e78–e140.

[19] Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol*. 2011;58:e44–e122.

[20] Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation*. 2006;113:e166–e286.